REMARKS

Entry of The Amendment of March 11, 2001: Entry of the Preliminary Amendment of March 11, 2002, Paper 9, is gratefully acknowledged. Claims 41, 4-5 and 10-40 are currently pending.

Amendment of the Specification:

Applicant filed U.S. Patent Application Serial No. 09/547,506 (now U.S. 6,548,484B1) on April 12, 2000, the same day as the instant application, and incorporated the contents of that application by reference in its entirety, e.g. at page 37, line 8 and page 51, loine 20.

Amendment of the Claims:

Claims 41, 4-5, 10-11, 13-16, 19-20, 22, 24-25, 28-31, 33-40 stand amended to recite the claimed invention with more particularity by incorporating elements of dependent Claim 10 into independent Claim 41.

Restriction Requirement and The Claimed Invention: Respectfully, as set forth previously, Applicant traverses the restriction requirement. The claimed invention is not a process "for treating a neurological dysfunction" (Paper No. 9, Page 2, second line from the bottom and Page 3, second line). In particular, the claimed process is an organic synthesis method applicable to 2-amine and 2-amide drugs, set forth as follows: namely, "A method for improving the aqueous solubility and blood brain barrier penetrability of a drug" involving steps for "forming a covalent chemical N-linkage between the drug and a sugar or oligosaccharide" (Claim 41), i.e., "B, is an optional bridging hydrocarbon..." and "D, is a nitrogen amine or amide linked through single bonds with each of B and E". The claimed invention is, with particularity, restricted to A moiety drugs that are "cyclic, heterocyclic, aryl or heteroaryl... CNS-acting prodrugs", in this case, drugs that can be chemically bonded to form the reaction product of Formula I and of the dependent claims (Claim 1, as filed) therefrom.

Rejection of Claims 4-5, 11-20 and 23-40 Under 35 U.S.C. § 112, second paragraph

Claims 4-5, 11-20 and 23-40 stand amended to more particularly recite the invention.

Rejection of Claims 41, 4-5 and 10-40 Under 35 U.S.C. § 103

In general, the claimed invention relates to a class of 2-amine and 2-amide biologically active drug compounds set forth in TABLE A and TABLE B of the specification, many of which have poor aqueous solubility and are poorly penetrable at the blood brain barrier. The biological effects exerted by these drug compounds are dependent upon stereospecific spatial interactions of residues in the instant compounds with residues within one or more binding sites of cell surface receptors, transporters and/or enzyme proteins. These chemical interactions are known to involve hydrogen bonding, electrostatic charge, van der Waals and hydrophic interaction chemistries which operate only over short distances between properly spatially aligned chemical residues, imposing significant spatial restrictions upon the design of prodrug compounds. Binding site interactions also usually require reversibility, e.g. as quantified in a compound's dissociation constant (KD). Synthetic compounds which bind, but do not release, can often inhibit physiologically important natural mediators, i.e., leading to antagonism of important physiological processes or outright toxicity.

In particular, with regard to the instant dopamine elected species, stereospecificity is required for receptor binding, dopamine transporter binding and glucose transporter binding, i.e., as set forth in Applicant's specification (as filed), i.e., Background of the Invention see the specification at page 3, last paragraph through page 7, first paragraph; and, as amended.

The claimed invention (after amendment) relates to conjugation of: (a) a native cyclic drug "A" selected from TABLE A or TABLE B, i.e., relatively unmodified with respective to charge or structure except for the conjugation residues; b) through a bridge linkage with specified chemistry including the lack primary side-chain charged residues which could interfere with binding interactions; and, c) to a relatively native saccharide residue, i.e., again unmodified except for the conjugation residues. The claimed invention assures that a drug and a saccharide constituent are preserved to enable binding interactions with receptors, transporters and enzymes in a conjugate compound that has both improved aqueous solubility and blood brain barrier penetrability. It is known by those of ordinary skill in the chemical arts that activation of the cyclic compounds appearing in TABLE A and TABLE B, e.g. for electrophilic or nucleophilic substitution/conjugation, can often be difficult because of electron withdrawing/donating residues either in the ring or as ring

substituents. Similarly, protective blocking and unblocking of charged residues critical for binding interactions can be difficult to accomplish without introducing significant structural modifications.

Thus, the conjugation chemistry relied upon by the Office in forming the basis for its rejection does not result in, nor does Applicant believe it renders obvious, the product compounds of Formula I (Claim 41).

In forming the basis for its rejections the Office has relied upon Likhoshersfov et al., 1998 in view of Mizuma et al. (Document ID #72 and #73); Takata et al. (Document ID #96); and, Vannucci et al. (Document ID #99).

Likhoshersfov, L.M., Novikova, O.S. and Shibaev, V.N. 1998. Akademii Nauk, Seriya Khimicheskaya 47 (6): 1214-1217 in the translated abstract supplied by the Office reportedly discloses use of N-chloroacetyl-β-glycopyranosylamines for "alkylation" of "piperazine, 2-phenethylamine, tryptamine and important biogenic amines (norephedrine, octopamine, dopamine)" (abstract, lines 1-8) reportedly "incorporating carbohydrate residues". The chemical structure as set forth, however, is not any of these drug compounds but instead rather a more chemically reactive morpholine moiety; and, the sugar is not a β-glycopyranosyl simple sugar but instead "N-(4-O-beta-D-galactopyranosyl-beta-D-glucopyranosyl"- (lines 15-16 of the abstract), i.e., a more stable lactose-like disaccharide. Likhosherstov et al., 1996 reportedly disclose N-chloroacetyl-β-glycopyranosylamine derivatives of lactose. If an N-chloroacetyl lactose disaccharide was used as a starting material for the morpholine conjugation, mutarotation has apparently occurred and the galactosyl ring is inverted about the glycosidic -O- bond, i.e., as indicated by the inverted positions of the hydroxyl residues recorded in the optical rotation (R and S) measurements of the glucosyl and galactosyl rings. The anomeric structure is not disclosed, e.g. whether the resultant modified disaccharide resides in an energetically stable chair or less stable skew or boat conformation. Biological activity of the resultant compound is also not disclosed, i.e., either in respect to the aglycon (morpholine) or glycon moieties. In the disclosed chemical structure, the bridging alkyl-carbonyl-amide moiety connects the relatively reactive morphilino-nitrogen atom to the glucosyl sugar moiety at the C_1 position in the sugar, i.e., eliminating the C_1 glucosyl hydroxyl residue. Any

requirements for blocking and unblocking are not disclosed in the abstract. Chemical stability of the acetylamide bridge and potential side reactions are not disclosed in the abstract, but it would seem to one of ordinary skill that the carboxy residue represents a potential site for electrophilic or nucleophilic addition. The reaction chemistry would seem to require attack on the activated N-chloroacetyl- residue, e.g. by the morpholino nitrogen atom. In the case of compounds like dopamine (or carbidopa), the resultant bridge moiety might therefore be expected to contain two nitrogen atoms, i.e., one derived from the N-chloroacetyl group and the second derived from the alkylamine of dopamine or carbidopa, and three (or four) carbon atoms, i.e., two derived from the N-chloroacetyl group and one (or two) from dopamine (or carbidopa).

Morpholine, disclosed in the chemical structure of Likhosherstov et al., is not a CNS drug or a drug having poor blood brain barrier penetrability or a biologically active compound capable of binding to a receptor, a transporter or an enzyme. There is no reason apriori to assume that a product compound of the method disclosed by Likhosherstov et al., with potential for altered anomeric glycosyl structure, charged and potentially reactive carboxy-alkyl side chain and potential presence of two nitrogen atoms, would act as a pro-drug that would be capable of binding to any of a transporter, a receptor or a prodrug activating tissue enzyme. Applicant does not believe that the methods of Likhosherstov et al. result in, nor render obvious, the methods and products of the claimed invention.

Mizuma et al., Document #72 discloses studies of p-nitrophenyl-β-D-glucopyranoside and β-naphthyl-β-D-glucopyranoside (reportedly obtained from Sigma Chemical Company, St. Louis, MO; page 2037, left column, "Materials and Methods" section, line 6) in everted-sac rat small intestine *ex vivo* in a Krebs-Ringer bicarbonate solution containing the respective glycoside. Transport from mucosal to serosal surface was reportedly determined by HPLC using a UV detector (at 302nm), i.e., for p-nitrophenyl-, and a fluorescence detector (excitation at 274nm and emission at 343nm), i.e., for β-naphthyl. Data expressed as "Absorption Clearance" was determined by dividing the observed absorption rate by the glycoside concentration at the mucosal side (page 2037, right column, last line), i.e., resulting in expression of values as μl/min/cm of intestine. Measured against high background levels of everted sac leakage, i.e., 0.7-0.8 μl/min/cm for non-transportable mannosyl and

glucuronidyl conjugates, the investigators reported values from a low of 1.04 μl/min/cm for β-naphthyl-galactosyl conjugates to a high of 4.45μl/min/cm for para-nitrophenyl-glucosyl conjugates. Non-everted sac controls, if included, were not disclosed. From these data it is difficult to calculate the molar amounts of drug that are involved in the alleged transport reactions, thus, whether the observed transport of potentially cell toxic p-nitrophenyl or β-naphthyl compounds (Arita et al., Doc. ID No. 3, PTO-1449, November 13, 2000) is in any way useful in drug delivery.

The investigator's stated conclusion was as follows: namely,

> "We conclude that conjugation of D-glucose and D-galactose to test compounds resulted in active adsorption in the intestine by the glucose transporter system, due to availability of the sugars on the glucose transport carrier. Further studies are required to determine the extent of the improvement in intestinal absorption by conjugation of glucose or galactose to non- or poorly absorbable drugs." (page 2039, left column, last paragraph).

Mizuma et al., Document ID#73, discloses additional studies of p-nitrophenyl α- or β-glucopyranoside or p-nitrophenyl- α- or β-galactopyranoside (reportedly obtained from Sigma Chemical Company, St. Louis, MO; page 1520, left column, "Materials and Methods" section, line 6) in the rat intestinal everted sac model of Mizuma et al., #72. Showing the limitations of this particular model, Mizuma et al. #73 attempted to limit observed hydrolysis of compounds at the mucosal surface of the everted intestinal sacs used continuous perfusion in a partially successful attempt to remove hydrolysis product of theoretically non-transportable p-nitrophenyl-α-glucopyranoside (i.e., page 1522, right column, "Serosal appearance of aglycone after absorption of p-NPαglc by mucosal perfusion"). Results disclosed in Table 1 are "μl/min/cm", i.e., as in Mizuma et al., #72 (above), but in Figure 2 results are expressed in "nmole/10cm of intestine/20 min" wherein absorption values are disclosed of for p-nitrophenyl-β-glucopyranoside of about 140-150 nmole/10cm/20 min (Fig.2, page 1521 and Fig.3, page 1522). For a rat, 10cm of intestine (about 4 inches) seems to involve a substantial amount of tissue and absorptive surface. In view of this seemingly large surface and the 20 minute incubation period, one of ordinary skill in the art might be lead to believe that 140-150 nanomoles is a relatively small amount of delivery achievable using this approach. Thus, Mizuma et al., #73 might be considered to teach away from that which Applicant has invented.

Applicant respectfully traverses the characterization by the Examiner that:

> "Mizuma et al. teaches that sugar-conjugated drugs such as glucose-conjugated compounds provide these compounds (drugs) with a new route by the way of the glucose transport carrier for better absorption in intestine, improving the poorly absorbable drugs (see abstract)." (page 5 of Paper No. 16, 5th paragraph).

The aglycon compounds p-nitrophenyl- and β-naphthyl- in Mizuma et al. #72 are not "drugs", are not poorly soluble, are not normally administered as "drugs", are not "poorly absorbable drugs", are not CNS active drugs, are not drugs selected "from TABLE A or from TABLE B" (Claim 41) and do not anticipate a product compound of "Formula I" (Claim 41). Mizuma et al. Document ID #72 is, at best, by author's own admission, an invitation to try future experimentation. Legal precedent for examination of claims under 35 U.S.C. § 103 directs that "obviousness must be certain" and not merely an invitation to try.

Takata et al., ID No. 96, and Vannucci et al., ID No. 99, disclose aspects of the cytological distribution of certain glucose transporters in different tissues including the brain and central nervous system. Takata et al. and Vannucci do not disclose chemical structures, synthesis methods or chemical structural design requirements for accessing these potentially available transporters nor provide guidance as to how the deficiencies in Likhosherstov et al. and Mizuma et al. (supra) may be cured by one of ordinary skill in the art.

The Federal Circuit *In re O'Farrell* examined a prior publication containing a written prophetic suggestion and provided the following instructions on predictability and apparent obviousness (emphasis added):

> "Obviousness does not require absolute predictability of success. Indeed, for many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice. There is always at least a possibility of unexpected results, that would then provide an objective basis for showing that the invention, although apparently obvious, was in law nonobvious..." In re O'Farrell, 853 f.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988).

In re Eli Lilly & Co. the Federal Circuit instructed:

> "An 'obvious-to-try' situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to

obtain the desired result..." In re Eli Lilly & Co., 942 F.2d 943, 14 USPQ2d 1056 (Fed. Cir. 1990).

In re. Epstein, the Federal Circuit instructed that printed publications

> "...must be enabling, thus placing the alleged disclosed matter in the possession of the public." In re. Epstein, 32 F.3d 1559, 31 USPQ2d 1817 (Fed. Cir. 1994)

See also Beckman Instruments, Inc. v. LKB Produkter AB, 892 F.2d 1547, 13 USPQ2d 1301 (Fed. Cir. 1989):

> "References relied upon to support a rejection for obviousness must provide an enabling disclosure. That is to say, they must put the claimed invention in the possession of the public."

Information Disclosure Statement:

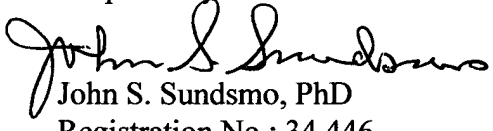
Issues raised in interpreting the Likhosherstov et al. 1998 abstract (supra) suggest that some clarification might be gained from the abstract of Likhosherstov et al. 1996.

Likhosherstov et al. 1996, Document ID No. 107 reportedly discloses synthesis of N-chloroacetyl-β-glycopyranosylamines from monosaccharides and lactose.

CONCLUDING REMARKS

In light of the amendments to the claims and remarks, removal of the rejections under 35 U.S.C. § 112 and 35 U.S.C. § 103 is respectfully requested. If any issues remain which can be expeditiously addressed in teleconference, the Examiner is urged to contact Applicant's agent at 760-806-3385 (office) or 615-423-3850 (mobile).

Respectfully submitted:



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TITLE	Synthesis of N-chloroacetyl-β-glycopyranosylamines, derivatives of monosaccharides and lactose
AUTHORS	Likhosherstov, L. M.; Novikova, O. S.; Shibaev, V. N.; Kochetkov, N. K.
SOURCE	*Russ.Chem.Bl.* 1996, **45:** 7 1760-1763
ORIGINAL SOURCE	*Izv.Akad.Nauk Ser.Khim.* 1996, : 7 1848-1851
DOCUMENT TYPE	Journal
CODEN	RCBUEYIASKEA
LANGUAGE	ENRU
CNR	6056454
ABSTRACT	N-Cloroacetyl-β-glycopyranosylamines were synthesized from various monosaccharides (hexoses, pentoses, deoxysugars, uronic acids, and sugar phosphates) and a disaccharide (lactose) by N-acylation of the corresponding β-glycosylamines with chloroacetic anhydride in DMF.In some cases, treatment of monosaccharides with NH3 in the presence of (NH4)2CO3 in MeOH or aqueous MeOH was more efficient than the methods previously described, as it gave β-glycosylamines in higher yields. - Keywords: β-glycopyranosylamines, monosaccharides, lactose, N-chloroacetylation, glycoconjugates
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